Patent
Attorney's Docket No. 032425-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of
Marshall S. Horwitz et al)

Application No.: 09/132,231) Group Art Unit: 1632

Filed: August 11, 1998) Examiner: J. Brusca

For: METHOD FOR PRODUCING NOVEL DNA SEQUENCE WITH BIOLOGICAL ACTIVITY)

DECLARATION OF PHILLIP A. PATTEN

I, Phillip A. Patten, solemnly swear and attest to the truth of the following:

(1) I am the same Phillip A. Patten who previously filed a Declaration Pursuant to 37 C.F.R. §1.608 in the above-identified application. I understand that Horwitz et al. have requested that an interference be declared between the claims in this application, and claims in several patents by Kauffmann et al. ("the Kauffmann patents").

(2) I understand that the Examiner of this application has taken the position that "the Kauffman applications do not disclose fully random peptide sequences, because the term stochastic used and claimed by Kauffmann was never defined in the Kauffmann applications as meaning random, and the examples of stochastic sequences disclosed in the Kauffmann applications do not result in fully random sequences." In particular, the Examiner has maintained that the examples in Kauffmann U.S. Patent No. 5,723,323 ("the '323 patent") result in sequences that are not fully random.

(3) I also understand that the Examiner is specifically referring to the Example in the '323 patent which begins at Column 5, line 25 and ends at Column 6, line 16. This Example describes a method for producing functional, novel DNA sequences using biological selection of random nucleotide sequences. In particular, this example describes "Stochastic Synthesis Using the Enzyme Terminal Transferase (TdT)." This method involves the production of a DNA sequence which contains a 5'-randomized sequence, a central "non-random" sequence, and a 3' randomized sequence. The DNA sequence is generated by adding "four kinds of deoxyphosphonucleotides, A, C, G and T from the two ends of an initially linearized expression vector, followed by formation of cohesive ends" (Column 1, lines 64-66 of the '323 patent), which can then be ligated to form a

"stochastic" stretch of DNA in the expression vector. The portion of this "stochastic" stretch of DNA which the Examiner maintains is not entirely random (i.e., "non-random") is the portion of the DNA sequence which constitutes the "cohesive ends" used to re-ligate the plasmid together. The cohesive ends are generated by the following protocol: (1) extending both random DNA strands on each end of the cleaved vector with TdT and dATP, (2) cleaning up the sample, (3) extending each of the strands with TdT and dTTP, (4) cleaning up the sample, (5) annealing the now complementary 3' end s to each other and (6) extending with polymerase. In this way, after religation of the plasmid, the following structure results:

---random DNA sequence---$(A)_n$ $(T)_m$---random DNA sequence---

---random DNA sequence---$(T)_n$ $(A)_m$---random DNA sequence---

(4) I have been asked to provide my comments on whether a person of ordinary skill in the art at the time of filing the original Kauffmann application would have considered the exact sequence of the "cohesive ends" (i.e., the stretch of A's bonded to the stretch of T's) to be important in generating Kauffmann's stochastic DNA sequences.

(5) It is my opinion that one of ordinary skill in the art at the time of filing the original Kauffmann application would not have considered the exact sequence of the "cohesive ends" to be important in generating Kauffmann's stochastic DNA sequences. The problem of cloning stochastic DNA sequences is analogous to the problem of cloning cDNA and the methods described are analogous to standard methods for tailing cDNA and cloning it into plasmid vectors. The cohesive ends described in the above-referenced example are merely used to recircularize the expression vector, so that the random sequence can be expressed and analyzed. Any short sequence of DNA can be generated for this purpose, as long as the sequences generated on each strand are complementary, i.e., they are able to bond to each other. As long as the sequences were generated such that A on one strand would bind to T on the other strand, and vice versa, and G on one strand would bind to C on the other strand, and vice versa, the plasmid could be recircularized so that the random DNA could be expressed. I believe the reason that Kauffmann chose to use A on one strand and T on the other strand, is that using TdT and a single type of nucleotide (i.e., A or T) on either strand, is the easiest way to accomplish the production of cohesive ends. Alternatively, Kauffmann could have used G on one strand and C on the other strand. The attached 1982 paper by Okoyama and Berg (Exhibit A) clearly outlines a protocol for cloning cDNA using A/T tails on the 3' end and G/C tails on the 5' e nd to achieve directional cloning. This method is also described in Maniatis, Fritsch and Sambrook, Molecular Cloning, Cold Spring Harbor Laboratory (1982) pp. 222-223, attached herewith as Exhibit B. Thus, the only requirement of the sequence the Examiner noted as "non-random" in Kauffmann's example is that the two ends of the two strands of DNA must be complementary so that they can bind to each other to recircularize the plasmid.

(6) I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any patent issuing therefrom.

6-28-01
Date

Phillip A. Patten